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THE STRUCTURE OF THE BRONCHO-ALVEOLAR SYSTEM WITH SPECIAL REFERENCE TO ITS FINE STRUCTURE*

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INTRODUCTION

The broncho-alveolar system is a canal system chiefly exercising respiratory functions and it is composed of the bronchial system which serves for the passage of air and the alveolar system which performs gas exchange. It has been shown by many investigators that the broncho-alveolar system plays an important role in the onset and the development of pulmonary diseases.

The present study was undertaken with the purpose of defining in greater detail the structure of the broncho-alveolar system and reexamining the pathogenesis of some pulmonary diseases.

I. MATERIALS AND METHODS

Materials used for this study were normal lung tissues and lesions that were experimentally produced in the lung. Pulmonary cancers of human being were also used in the present investigation.

India ink and tubercle bacilli were instilled into the trachea of rabbits. These animals were killed one hour to ten hours after instillation and their lungs were removed for fixation.

Mice of dd strain were given intraperitoneally 0.01 cc/gm of 10 per cent urethane solution, and sacrificed ten weeks after the injection. Pulmonary tumors induced by urethane were removed for fixation.

These tissues were fixed in 10 per cent formalin, embedded in paraffin and sections were made. The specimens were stained with haematoxylin-eosin, Weigert's elastic staining, silver impregnation and other special staining methods.

On the other hand, small blocks of tissues about 1 cubic millimeter were cut rapidly from the lung or pulmonary lesions, and fixed for one hour in 1 per cent osmium tetroxide fixative adjusted at pH 7.4 and isotonic with phosphate buffer containing sucrose. After several washings in phosphate buffer or water, the tissues were dehydrated in ascending concentrations of alcohol solutions and

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finally embedded in methacrylate. Thin sections were cut by the Hitachi microtome model UM-2 and examined with the Hitachi electron microscope model HS-6.

II. GENERAL OUTLINE OF THE BRONCHO-ALVEOLAR SYSTEM

A. Branching mode of the broncho-alveolar system

The bronchial tree repeats bifurcations in turn from trachea as main bronchus, lobar bronchus, segmental bronchus and subsegmental branchus until it turns into the terminal bronchiolus, the 7th branching from the segmental bronchus. In the more peripheral portions, it repeats bifurcations in turn from terminal bronchiolus, being primary respiratory bronchiolus, secondary respiratory bronchiolus and alveolar duct until it reaches the alveolus as shown in Fig. 1.

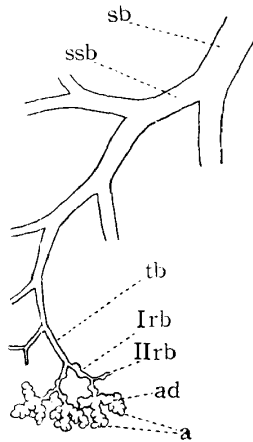


Fig. 1. Branching mode of the broncho-alveolar system.

sb: segmental bronchus, ssb: subsegmental bronchus,
 tb: terminal bronchiolus, Irb: primary respiratory
 bronchiolus, IIrb: secondary respiratory bronchiolus,
 ad: alveolar duct, a: alveolus.

B. Histological findings of the bronchial wall

The structure of the wall of a large bronchus is shown in Fig. 2, which can be divided into four layers of epithelium, submucosa, tunica muscularis and adventitia. Besides these, the mucous glands and the cartilage are observed in the wall.

1. Blood vessels of the bronchial wall

The blood vessels distributed in the bronchial wall are shown in Fig. 3. The bronchial artery runs through the adventitia along the bronchus from the pulmonary hilum and extends its small branches to the tunica muscularis and the submucosa. Networks of capillaries present an irregular polygonal form and the blood which flows from these capillaries mostly pours into the pulmonary vein through the intra-pulmonary bronchial vein, and partly into the V. azygos or the V. hemiazygos through the extra-pulmonary bronchial vein.



Fig. 2. Histological findings of the bronchial wall.

ep: epithelium, sm: submucosa, tm: tunica muscularis,
g: mucous gland, l: lymphatics, ad: adventitia,
alv; alveoli.

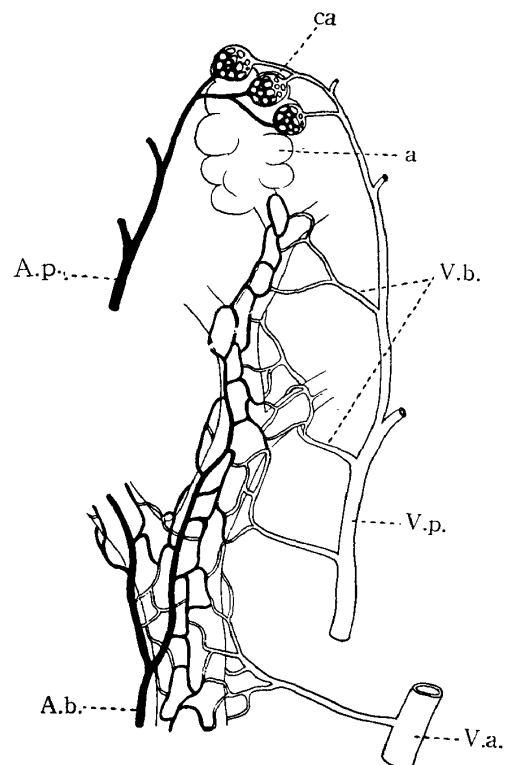


Fig. 3. Blood vessels of the bronchial wall.

A.p.: A. pulmonalis, V.p.: V. pulmonalis,
A.b.: A. bronchialis, V.b.: V. bronchialis,
ca: alveolar capillaries, a: alveolus.

2. Lymphatic system of the bronchial wall

As shown in Fig. 4, the lymphatics are not observed in the alveolar region, but are observed in the more proximal part than the terminal bronchiolus. The lymphatics form only a single layer of network in the submucosa of a small bronchus, but in the wall of a large bronchus that is provided with cartilages, they form a single layer of networks on both sides of the cartilage. The lymph from these networks of lymphatics flows into the hilar lymph nodes through collecting lymphatics accompanied by the bronchus.

Lymphoid tissues are scattered in the bronchial wall, and classified into three types corresponding to their sites: epithelial, propria and adventitia.

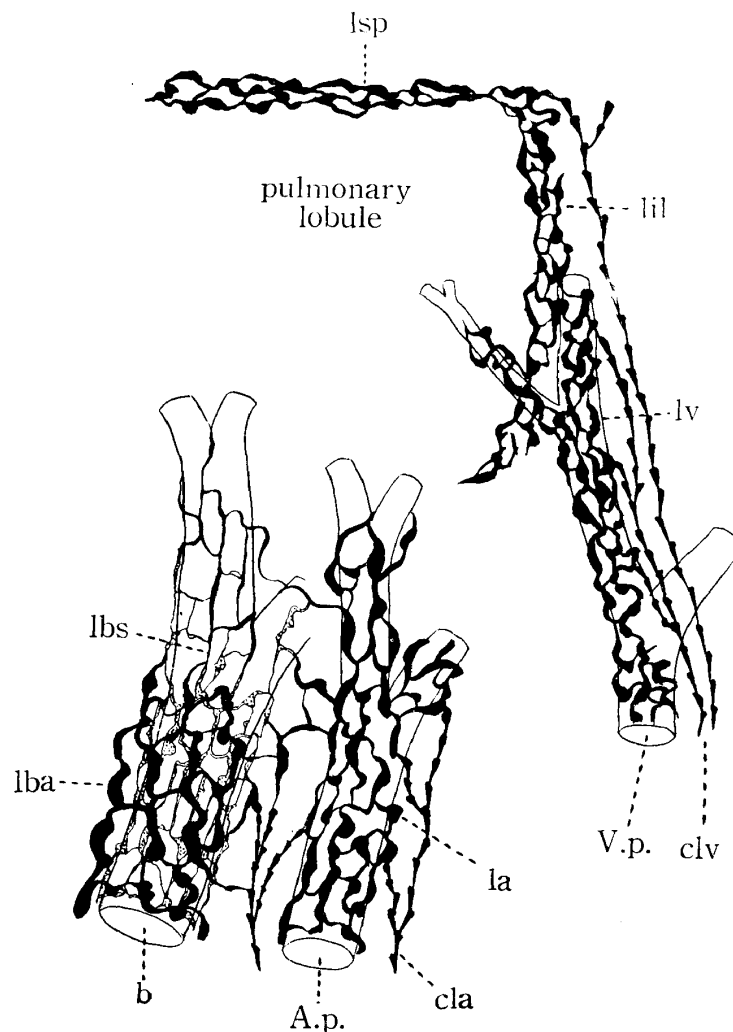


Fig. 4. Lymphatic system of the broncho-alveolar system.

lsp: subpleural lymphatics, lil: interlobular lymphatics, lv: lymphatics accompanied by the pulmonary vein, lbs: lymphatics in the submucosa, lba: lymphatics in the adventitia, la: lymphatics accompanied by the pulmonary artery, clv: collecting lymphatics accompanied by the pulmonary vein, cla: collecting lymphatics accompanied by the pulmonary artery, b: bronchus, A.p.: A. pulmonalis, V.p.: V. pulmonalis.

3. Nervous system of the bronchial wall

Anterior and posterior pulmonary plexuses in the pulmonary hilum are composed of nerve fibers and ganglions originated from vagal, sympathetic and phrenic nerves, as shown in Fig. 5. The nerve fibers which derive from these plexuses form extra-chondrial and sub-chondrial plexuses in the bronchial wall.

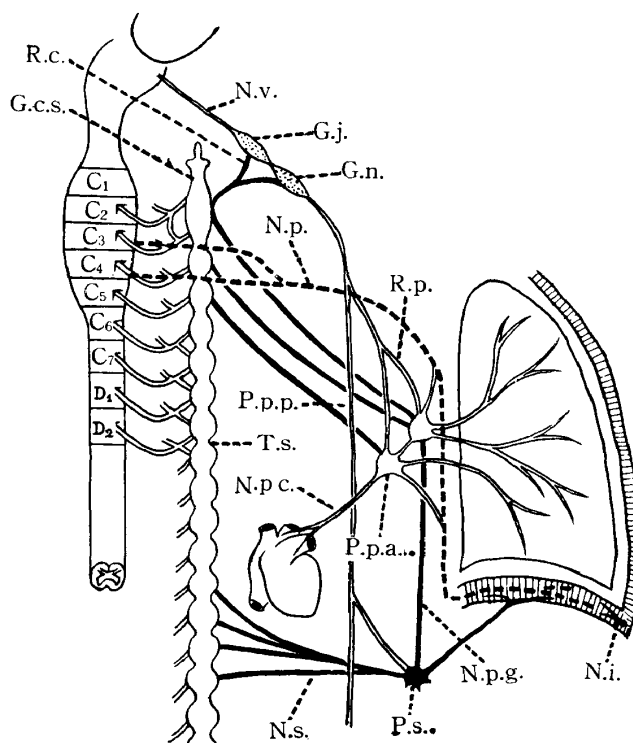


Fig. 5. Nervous system of the broncho-alveolar system.

N.v.: N. vagus, N.p.: N. phrenicus, N.i.: N. intercostalis,
 N.s.: N. splanchnicus, T.s.: Truncus sympathicus,
 P.p.p.: Plexus pulmonalis posterior, P.p.a.: Plexus pulmonalis
 anterior, P.s.: Plexus solaris, N.p.c.: N. pneumocardiacus,
 N.p.g.: N. pneumogastricus, G.j.: Ganglion jugulare,
 G.n.: Ganglion nodosum, G.c.s.: Ganglion cerv. sup.,
 R.c.: Rami communicantes, R.p.: Rami pulmonales.

Afferent sensory nerve fibers from the bronchial system, that is, visceral sensory nerve fibers originate from the epithelium, the submucous tissues, the smooth muscles and the alveolar walls. Efferent motor nerve fibers, that is, vegetative nerve fibers terminate in the mucous glands, the smooth muscles and the alveolar walls.

III. ULTRASTRUCTURE OF THE BRONCHO-ALVEOLAR SYSTEM

A. Ultrastructure of the bronchial system

The bronchial epithelium is a columnar ciliated epithelium and composed of three kinds of epithelial cells: ciliated, goblet and basal cells as shown in Fig. 6.

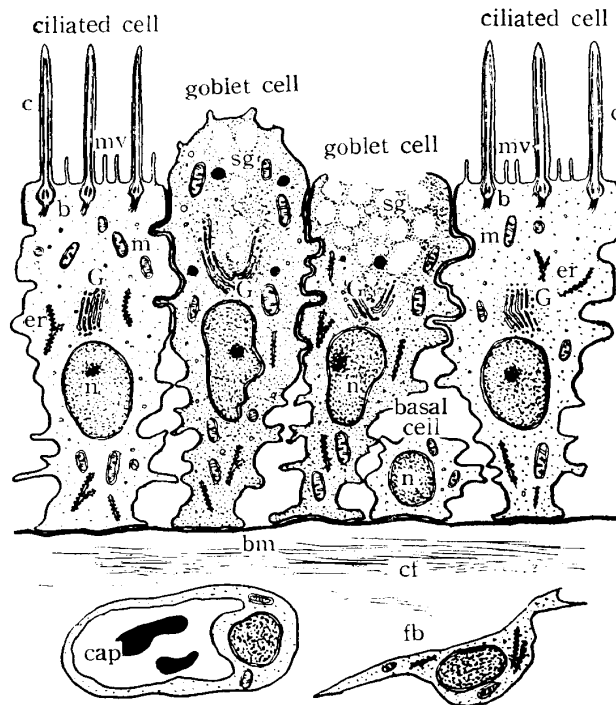


Fig. 6. Ultrastructure of the bronchial epithelium.

c : cilia, mv : microvilli, b : basal bodies, m : mitochondria, n : nucleus, er : endoplasmic reticulum, G : Golgi's complex, sg : secretory granules, bm : basal membrane, cf : collagen fibers, cap : capillary, fb : fibroblast.

Numerous cilia and microvilli can be seen on the surface of the ciliated cells as shown in Fig. 7. Microvilli are nothing but filiform projections of cytoplasm. However, the cilium contains several filaments in it. In other words, two pairs of central filaments and nine pairs of peripheral filaments are seen arranged in the cilium, and they are transformed into basal bodies at the base. The structure of the basal body resembles that of the centriole and it seems to have something to do with the movement of the cilium.

Many mitochondria and endoplasmic reticula are included in the cytoplasm of ciliated cells and there sometimes even Golgi's complexes are seen.

The goblet cell is devoid of cilia as shown in Fig. 7, and fine granules are densely distributed in its ground substance. The vacuole-like structure is observed in this cell and it is called "secretory granule" or "mucous granule". The number and the size of the granule are changeable and this may be interpreted as the various stages of mucous production. The theory as to the origin of these mucous granules has not yet established, but it seems that Golgi's complex has much to do with their production.

Basal cells are the small cells in the basement of the epithelium as shown in Fig. 8 and their cytoplasm has no particular features.

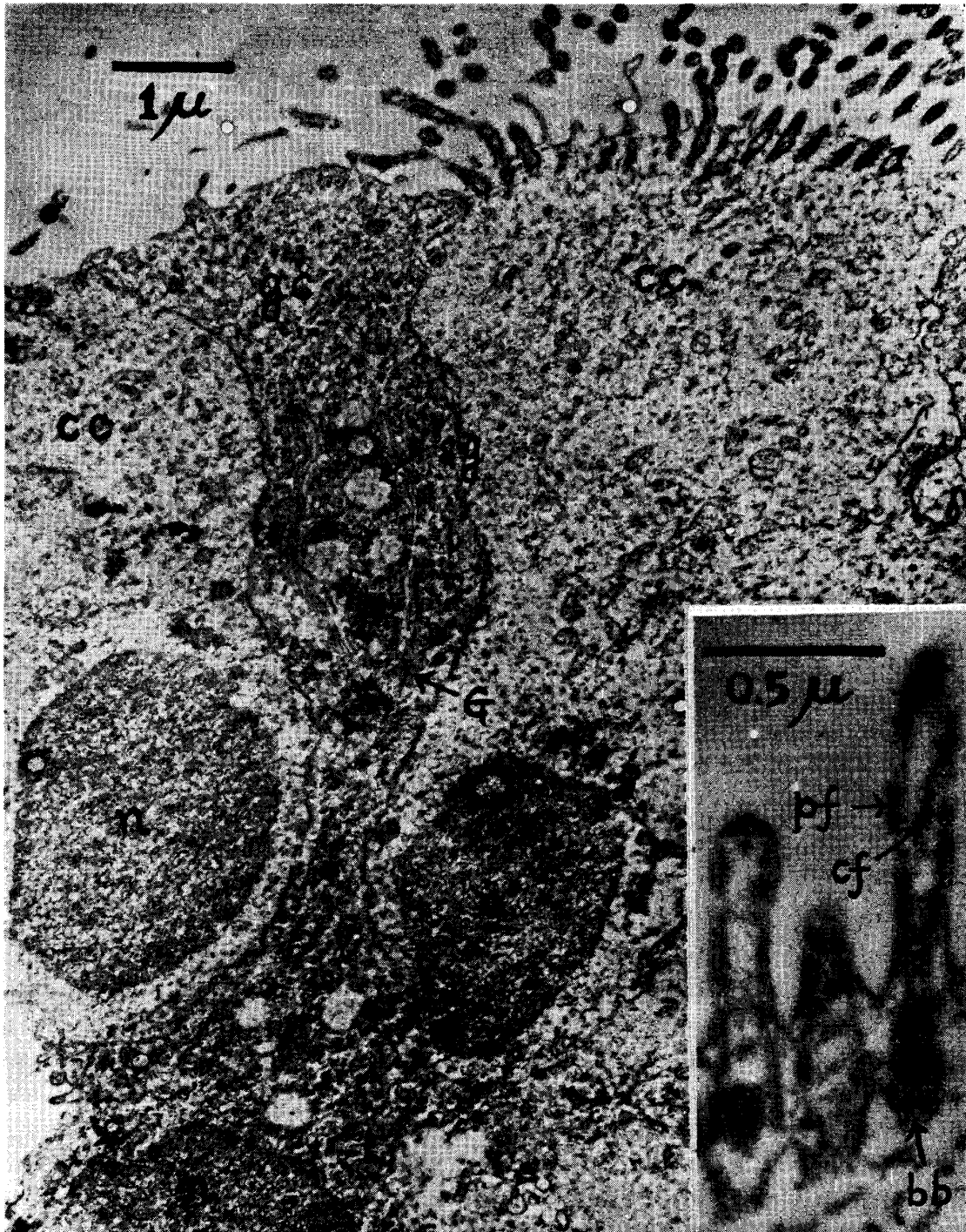


Fig. 7. Epithelial cells of the bronchial wall.

cc: ciliated cell, gc: goblet cell, sg: secretory granules,
G: Golgi's complex, bb: basal body, cf: central filament,
pf: peripheral filament, n: nucleus.

The part which is histologically called as a "basal membrane" means the wide portion stained under the epithelium by silver impregnation. On the contrary,

the portion which is electron microscopically called as a “basal membrane” is a very thin layer directly under the epithelium as shown in Fig. 8 and is quite different from the former.

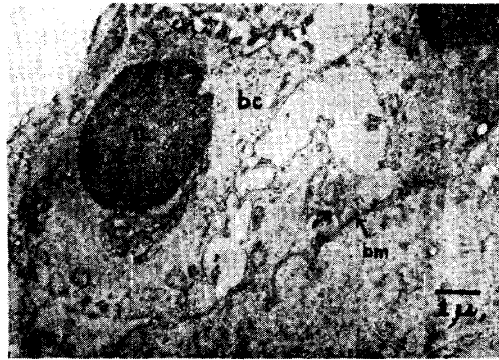


Fig. 8. Basal cell and the basal membrane.

bc: basal cell, bm: basal membrane, n: nucleus.

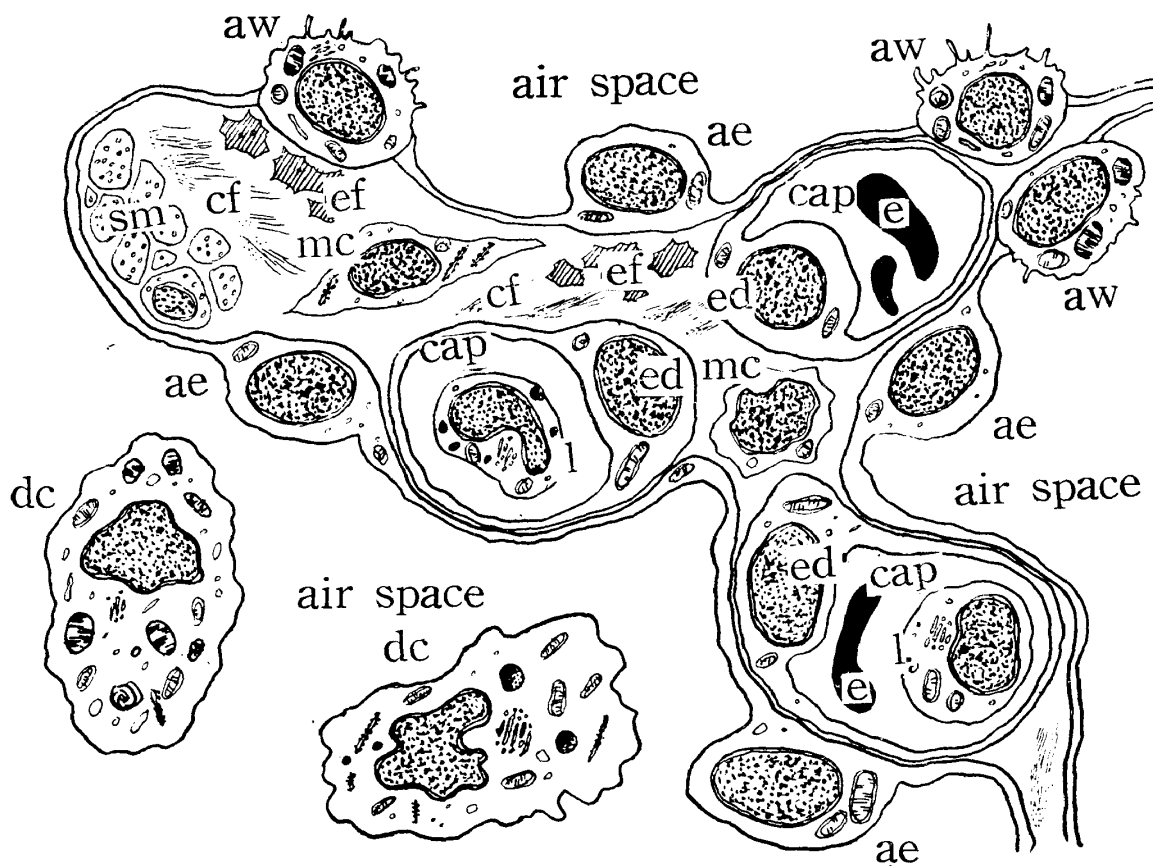


Fig. 9. Ultrastructure of the alveolar region.

ae: alveolar epithelium, aw: alveolar wall cell, dc: dust cell, ed: endothelium, cap: capillary, e: erythrocyte, l: leucocyte, mc: mesenchymal cell, sm: smooth muscle, cf: collagen fibers, ef: elastic fibers.

B. Ultrastructure of the alveolar region

The alveolar wall is electron microscopically covered continuously with two kinds of cells as shown in Fig. 9. One is the alveolar epithelial cell and the other is what we call the alveolar wall cells.

As Fig. 10 shows, the alveolar epithelial cell is thick in the area of the nucleus and covers the alveolar wall like outspread wings. The thinnest part is about 0.2 microns. The cytoplasm contains few organellae.

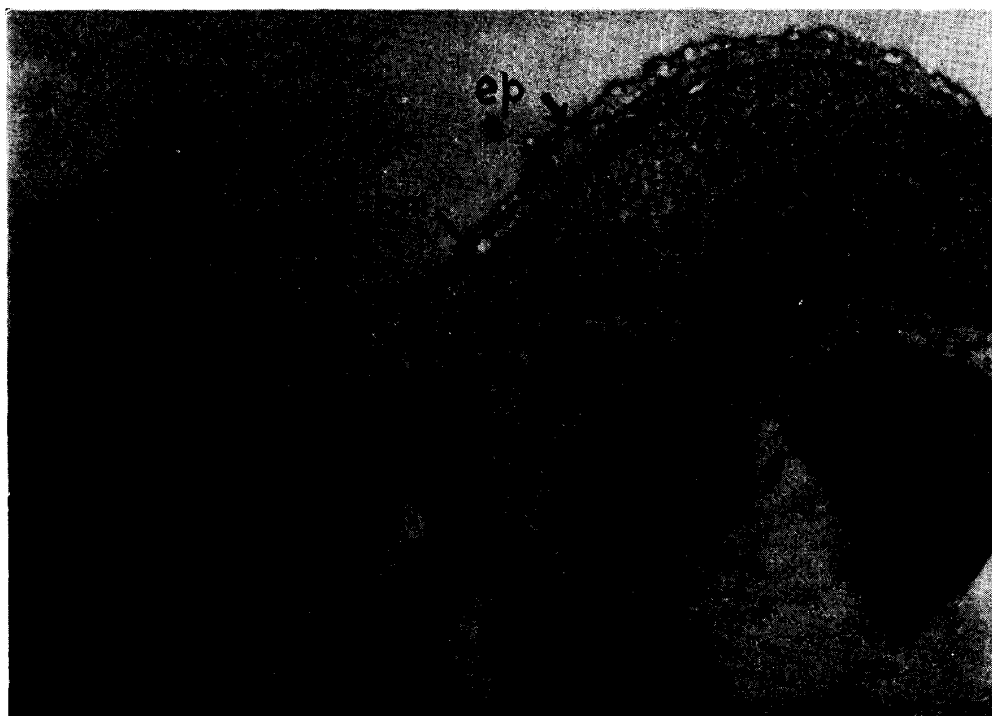


Fig. 10. Alveolar epithelium and the capillary endothelium.

ep: alveolar epithelium, ed: capillary endothelium,
n: nucleus of the epithelium, n': nucleus of the
endothelium, e: erythrocyte, l: leucocyte,
bm: basal membrane.

The alveolar wall cell is sometimes called the "B-type cell" or the "special cell" or the "large alveolar cell" as contrast to the alveolar epithelial cell. It does not have the filmy stretched part and often possesses a large number of microvilli at the surface facing the air space. Its distinction lies in that the alveolar wall cell has many "osmiophilic bodies" which reveals strong affinity to osmium as shown in Fig. 11.

These inclusion bodies have never been observed in the cells of other organs or tissues and appear to be peculiar to the alveolar wall cell. The osmiophilic bodies can be classified into three types as shown in Fig. 12. It is assumed that those of IIa type, which are mostly found, are originated by the transformation

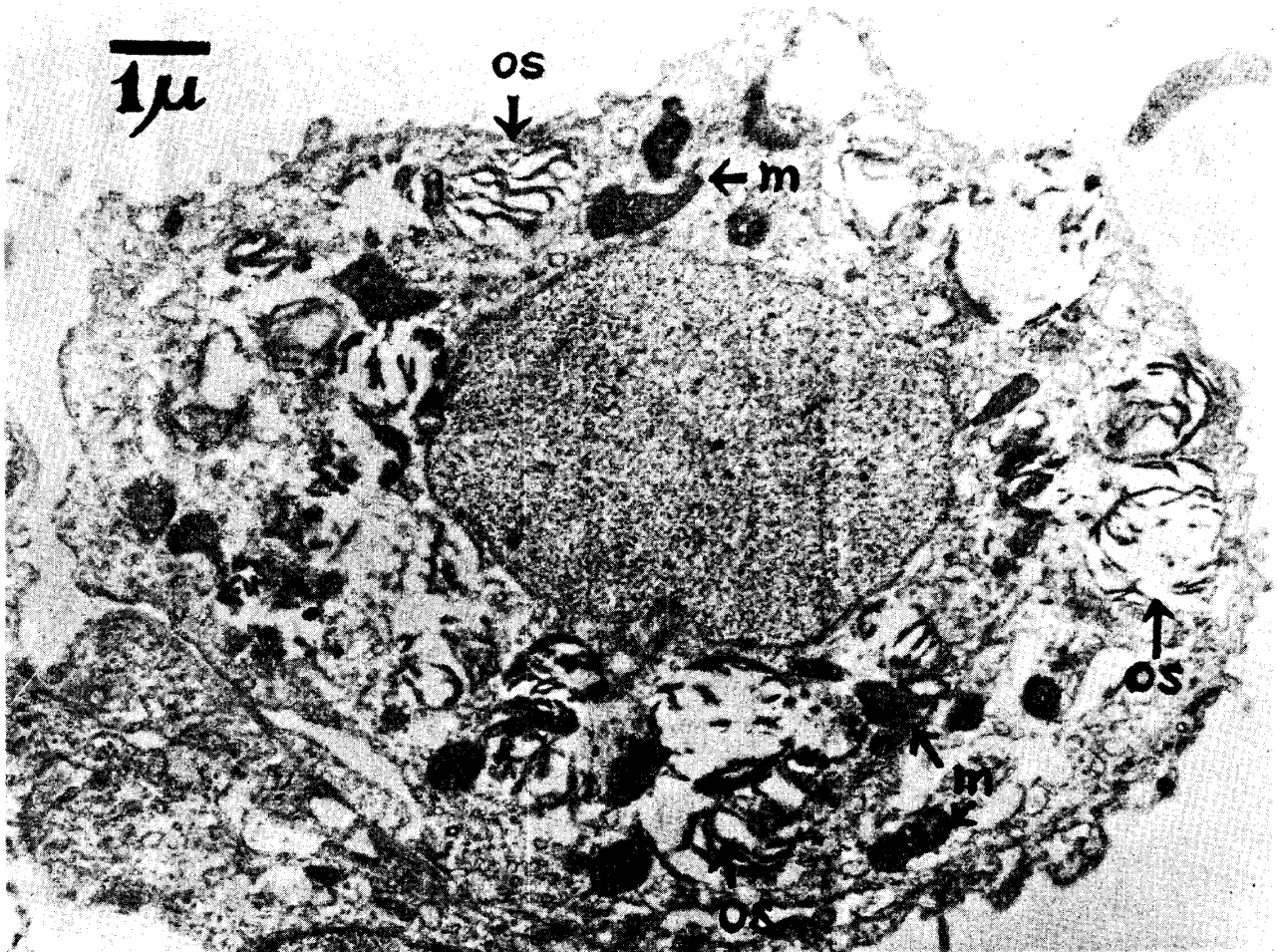


Fig. 11. Alveolar wall cell.

os : osmiophilic bodies, m : mitochondria.

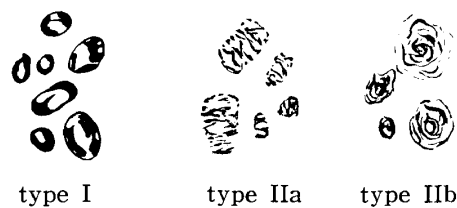


Fig. 12. Three types of the osmiophilic bodies.

of mitochondrias. Fig. 11 shown the transformation of mitochondrias to osmiophilic bodies.

As the origin of the alveolar wall cell, some assume it may be epithelial, while others as mesenchymal. The present authors would like to think it might be the epithelial origin. The reason why we think it is epithelial is that (1) the alveolar wall cell is quite similar to the alveolar epithelial cell in its cytoplasmic structures in the fetal lung as shown in Fig. 13, (2) the alveolar wall cell has also a basal

membrane and often microvilli, as do some bronchial epithelial cells and also (3) in lower vertebrates, particularly in amphibia, the alveolus is lined up with cells which have similar aspects to the alveolar epithelial cells of human lung having microvilli and the osmiophilic bodies as shown in Fig. 14.

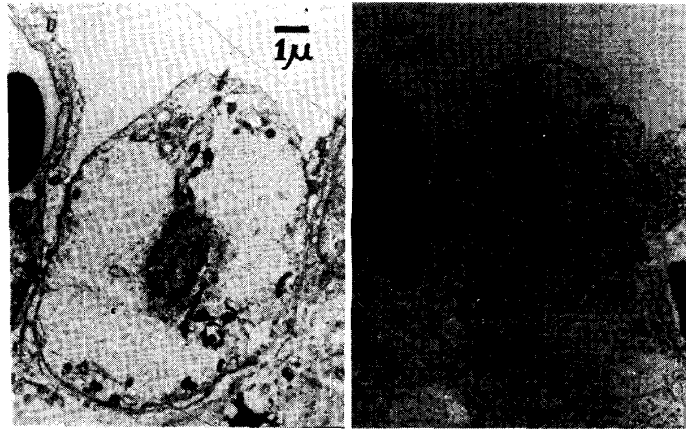


Fig. 13. Epithelial cells in the fetal lung.

The alveolar wall cell (left) is similar to the alveolar epithelial cell (right) in its cytoplasmic structure.



Fig. 14. Alveolar epithelial cell of the frog.

mv : microvilli, os : osmiophilic body,
cap : capillary, ed : endothelium.

Judging from these findings, it is considered that the alveolar epithelial cell is so flat in its shape as to be convenient for gas exchange, while the alveolar wall cell is of epithelial origin and has the shape similar to that of the bronchial cell even in the alveolar region.

Endothelial cells of the blood capillary of the alveolar wall extend as a thin membrane and, the blood are therefore in contact with the alveolar air space through a very thin layer of cytoplasm.

In addition to the previously mentioned cell, many collagen fibers, elastic

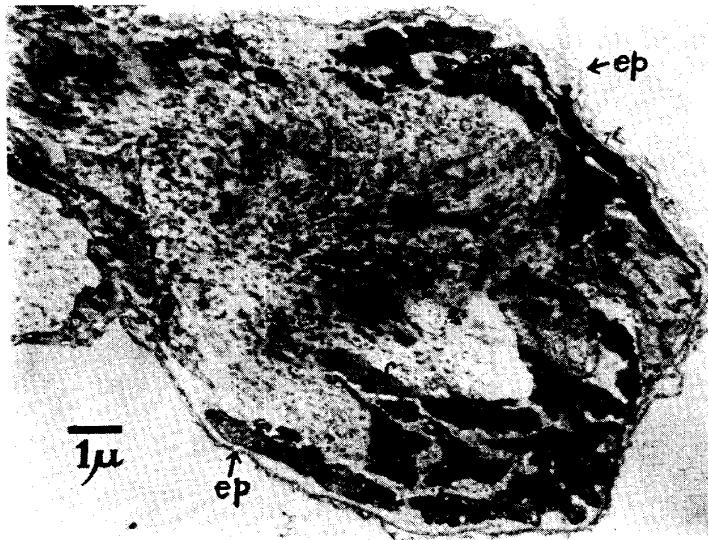


Fig. 15. Mesenchymal tissues of the alveolar septum.

ep: epithelium, sm: smooth muscles,
cf: collagen fibers, ef: elastic fibers.

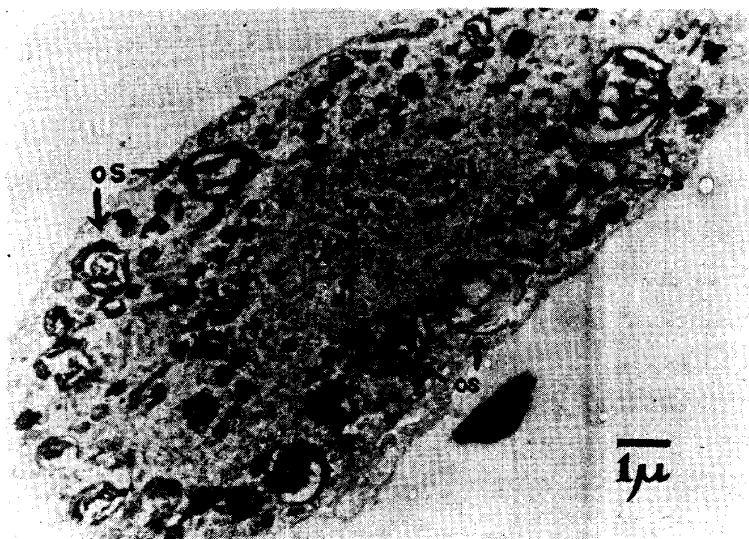


Fig. 16. Dust cell which has osmiophilic bodies.

os: osmiophilic bodies.

fibers and some mesenchymal cells are present within the alveolar septum as shown in Fig. 15.

Two types of free cells are observed in the alveolar space and each appears to have a different origin. As shown in Fig. 16, one has osmiophilic bodies in

its cytoplasm and is considered to have originated from the alveolar wall cell. The other is devoid of osmiophilic bodies as shown in Fig. 17, and often typical Golgi's complexes. Since the latter has strong phagocytic properties and its form and structures are similar to that of the monocyte, the authors have assumed it to have originated from the monocyte.

In short, there seem to be two types of dust cells, one of which originates from alveolar wall cells, and the other from monocytes.

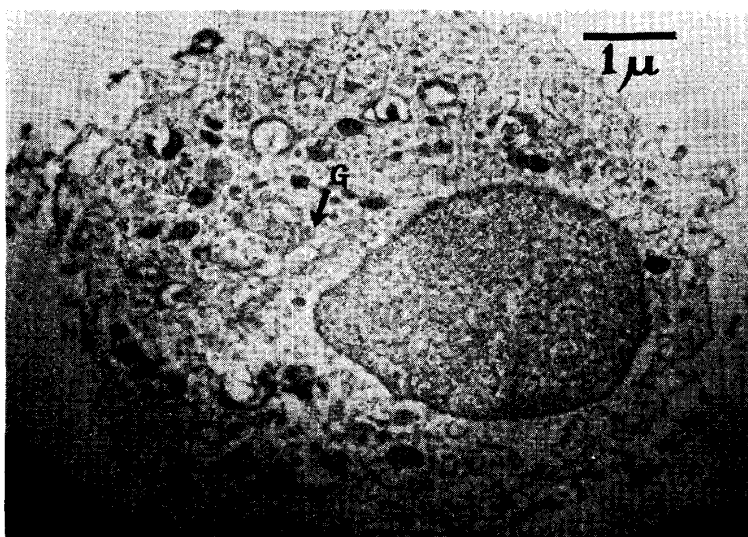


Fig. 17. Dust cell which is devoid of osmiophilic bodies.
G: Golgi's complex.

IV. SOME PROBLEMS RELATING TO THE ULTRASTRUCTURE OF THE BRONCHO-ALVEOLAR SYSTEM

A. Problems relating to inflammation

As to inflammation, the authors have studied experimentally the disposal of foreign bodies and bacteria from the broncho-alveolar system.

The healthy bronchial epithelium does not permit the invasion of particles of India ink and bacteria into the tissues of respiratory tract. But they are absorbed only at the places where there are the epithelial type lymphoid tissues are on the bronchial wall.

These epithelial type lymphoid tissues belong to the so-called "extravasculäres Saftbahnsystem (KIHARA)". The particles of India ink and bacteria which are absorbed through these tissues are immediately carried to the hilar lymph nodes through the peribronchial lymphatics.

In alveolar region also, the healthy epithelial tissues of the alveoli prevent invasion, these foreign bodies being disposed of through phagocytosis by the dust cells of the monocytic system in the alveolus. Fig. 18 shows phagocytosing

dust cells, many particles of India ink, and Fig. 19 shows the dust cell that is going to engulf tubercle bacilli. After these particles and bacilli are phagocytosed by a dust cell, they are carried from the dent of the cell membrane to the smooth surfaced endoplasmic reticulum.

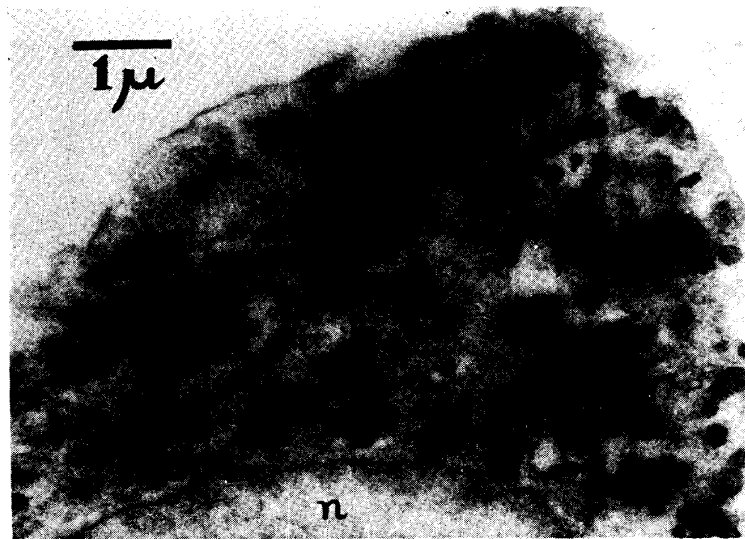


Fig. 18. Phagocytosing dust cell.

Many particles of India ink are seen in the endoplasmic reticulum.

n: nucleus, G: Golgi's complex.



Fig. 19. Dust cell that is going to engulf tubercle bacilli.

tb: tubercle bacilli.

Cell reaction generally comes to an end at this stage when India ink is injected, but in the case of injection of tubercle bacilli, many leucocytes exude

in the alveolar space after the reaction of the dust cells and then non-specific inflammation sets in as shown in Fig. 20.

It means that the first non-specific inflammation against foreign bodies or bacteria is not caused in the tissues of the bronchial and alveolar wall, but sets in as exudation of cells which propagate themselves over the alveolar space.

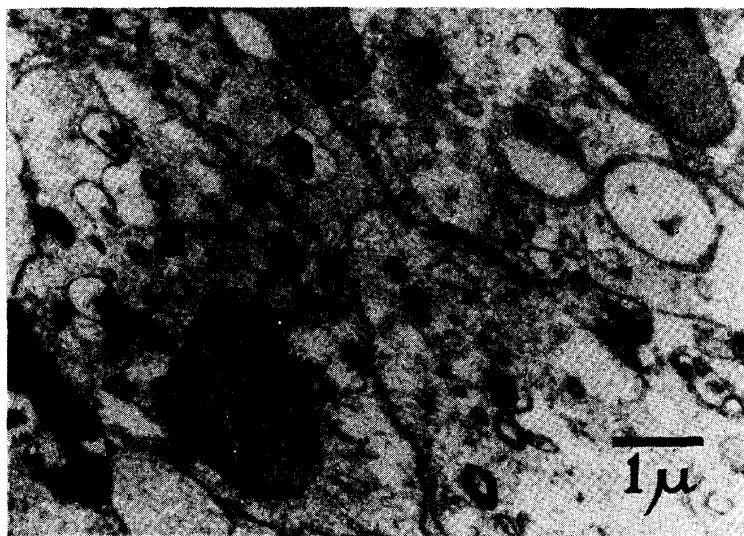


Fig. 20. Exudation of leucocytes in the alveolar space.

B. Problems relating to pulmonary tumors

When urethane is injected into the peritoneal cavity of a mouse, pulmonary tumors are caused in a few weeks. Judging from the investigation of serial sections, most of these tumors do not seem to be related directly to the bronchial epithelium, but appear to have originated from the alveolar region.



Fig. 21. Pulmonary tumor induced by urethane.

Two ciliated cells are seen in this figure.

Whether alveolar epithelium exists or not has long been a point of discussion, and accordingly it has not been finally concluded whether epithelial tumors can originate from the alveolus or not. It seems highly reasonable, however, to



Fig. 22. Tumor cells induced by urethane.

A tumor cell cotaining osmiophilic bodies is seen in this figure
os: osmiophilic bodies, m: mitochondrias.

assume that the tumors of epithelial origin can originate from the alveolus, since it is now apparent that alveolar epithelium does exist. In addition, the finding of peripheral pulmonary tumors following the application of urethane supports this presumption.

When viewed through the electron microscope, a pulmonary tumor induced by urethane is observed to be composed of cuboidal cells as shown in Fig. 21, among which some cells similar to ciliated cells of the bronchus are often seen. Besides, some tumor cells containing osmiophilic bodies are often seen among them as shown in Fig. 22.

Therefore, it is evident that some cells similar to bronchial epithelial cells and to alveolar wall cells are involved in the same tumor.

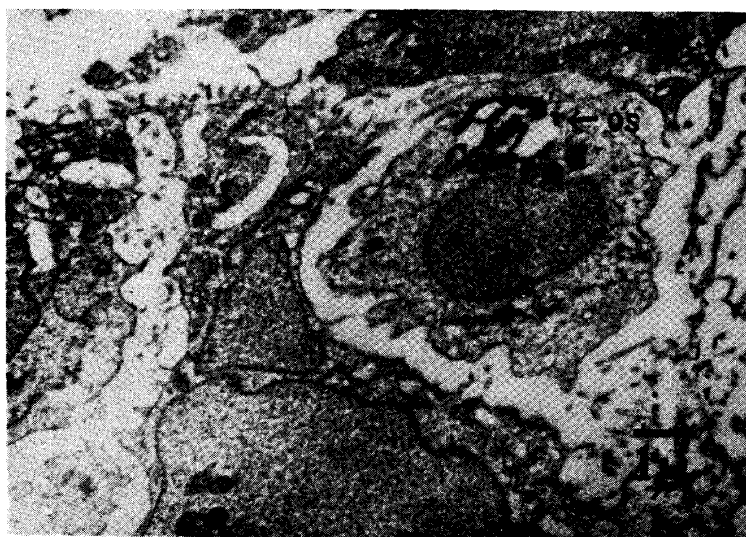


Fig. 23. A cell containing an osmiophilic body in a human lung cancer.

os : osmiophilic body.

The authors also made electron microscopic observations of some cases of human lung cancer. Although the cells of lung cancer were quite different in shape from the epithelial cells of the bronchus and the alveolus, the authors could find some osmiophilic bodies as shown Fig. 23. In the other words, in the tumor that is considered to be of bronchial origin, some cells similar to epithelial of the alveolus are observed and vice versa.

The bronchial epithelial cell has its own peculiar shape just as the alveolar epithelial cell does, but ontogenically and phylogenically speaking, they are of kinship and so it is natural that such a finding should be observed.

Many arguments have been repeated on the existence of the so-called "alveolar cell cancer" and there has been a tendency to distinguish by strict criteria bronchial cancer from alveolar cell cancer ; but the authors are of opinion

that these are to be considered as members of a common group from a higher cytological point of view.

SUMMARY

1) In the bronchial epithelium, three types of cell are revealed by electron microscopy, namely, ciliated cell, goblet cell and basal cell.

2) The alveolar wall is found to be covered continuously with two kinds of epithelial cells, namely, alveolar epithelial cell and alveolar wall cell.

3) There seem to be two types of dust cells, one of which originate from alveolar wall cell and the other from monocyte.

4) Non-specific inflammation against foreign bodies or bacteria sets in as exudation of cells into the alveolar space.

5) Some cells similar to bronchial epithelial cell and alveolar wall cell are involved in the same tumor induced by urethane.

6) In the tumor that is considered to be of bronchial origin, some cells similar to the alveolar wall cell can be found.

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